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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,423	07/31/2003	Masaya Tohyama	59150-8023.US00	3705

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EXAMINER	
KOLKER, DANIEL E	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 10/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/633,423	TOHYAMA ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-30* is/are pending in the application.

4a) Of the above claim(s) *24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-23 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *21-30* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's remarks and amendments filed 25 July 2005 and 29 August 2005 have been entered. Claims 1 – 20 and 31 – 262 are cancelled; claims 21 – 30 are pending.

Election/Restrictions

2. Applicant's election without traverse of Group II and species (h) in the reply filed on 25 July 2005 is acknowledged. Applicant has indicated that claims 21 – 23 and 25 – 31 read on the elected species. Applicant has also acknowledged which functional recitations of claims 25 – 26 and 29 read on this species.

3. Claim 24 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 25 July 2005.

Sequence Compliance

4. This application discloses an amino acid sequence which is not identified by SEQ ID NO:. The brief description of Figure 17 includes an amino acid sequence which is not identified by SEQ ID NO: in either the drawing or the brief description (see page 55, line 27). Applicant is directed to MPEP § 2422.02 which requires that all sequences beyond the minimum length set forth in 37 CFR § 1.821(b), even those presented in drawings, be identified by SEQ ID NO:. Applicant is requested to carefully review the specification to ensure that it complies with the sequence rules.

Information Disclosure Statement

5. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

6. Claims 25, 26, and 29 are objected to because of the following informalities: the claims recite multiple non-elected species of the present invention. In the remarks filed 25 July 2005 applicant indicated that the elected species reads on specific functional recitations of claims 25 and 26, and specific structures recited in claim 29. The elected species does not read on interactions between MAG and GT1b, or between GT1b and p75, recited in claims 5 and 6 or on nucleic acid molecules, p75 extracellular domains, Rho GDI polypeptides, or agents capable of interacting with those, for example. Appropriate correction is required.

7. Claims 27 and 28 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 7 recites the limitation "wherein the nerve regeneration is carried out *in vivo* or *in vitro*." This fails to limit claim 21 because it would be impossible for the composition to be used for inhibition of a p75 signal transduction pathway that is neither *in vivo* nor *in vitro*. Claim 28 fails to limit claim 21 as it appears to be a limitation of an injured nerve, but the parent claim does not recite a nerve.

Priority

8. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Japan on 28 March 2003. It is noted, however, that applicant has not filed a certified copy of the 2003-92923 application as required by 35 U.S.C. 119(b).

The examiner has cited prior/intervening art on the claims. Therefore the effective filing date of the pending claims is the date this application was filed, 30 April 2003. This date may be changed should applicant meet the requirements of 35 U.S.C. 119 (a) – (d) for foreign priority. See 37 CFR § 1.55(a)(3) and 1.55(a)(4).

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 21 – 23 and 25 – 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide SEQ ID NO:2 or anti-p75NTR antibodies, or Pep5 with an alanine residue added to the C-terminal end, or residues 273-427 of SEQ ID NO:4, does not reasonably provide enablement for all agents, unlimited by structure, which are capable of inhibiting p75 signal transduction pathways. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

The nature of the invention, an agent capable of inhibiting an intracellular signal transduction pathway, is complex. The claims are very broad in that with they include a plethora of species, many of which are defined only functionally and include no structural limitations. Thus a skilled artisan would have to undertake a very large degree of experimentation to make and use the compositions commensurate in scope with the claims. The artisan would essentially have to resort to trial-and-error experimentation in order to discover those agents which inhibit the p75 signal transduction pathway.

Claim 29 includes providing any variant or fragment of the compounds recited in an amount effective for regeneration. "Fragment" is defined very broadly in the specification (see p. 79 lines 6 – 35) and includes a single amino acid. Applicant has not provided working examples of compoistions which are single amino acids that inhibit p75 signal transduction, has not provided guidance to the artisan in the selection of which variants will function as inhibitors. The art indicates that the fragments of proteins involved in various aspects of p75 signal transduction pathways cannot be easily predicted, and involves a large degree of experimentation. Mukai et al. (2002. Journal of Biological Chemistry 277:13973-13982) teaches experiments by which nine fragments of NADE (the p75-NTR-associated death executor, a molecule which binds to the intracellular domain of the p75 receptor) were tested to see which ones were most likely to induce apoptosis. The results of the experiments with these fragments

are very complex. The percentage of cells which are apoptotic depends not only on the length of the fragment and which motifs of the protein is present, but also on the presence or absence of the p75NTR (see Figure 3 on p. 13976). Thus any nerve-regenerating effects of the instantly-elected Pep5 protein would not be expected to be retained in all fragments or variants of the protein, including the single amino acids that comprise the sequence, and the artisan would have to resort to a large degree of experimentation in an unpredictable complex field to determine which fragments would kill the cells and which would promote regeneration.

Claim 23 is limited to transduction agents which are either part of the p75 pathway or a variant or fragment thereof, or an agent which can interact with one of these. This is a very broad limitation, because the p75 pathway is very complex and includes many molecules, from the neurotrophin ligands to NF-kappa-B to theTRAF6 and Src (see Mamidipudi et al. 2002. Journal of Neuroscience Research 68:373-384, particularly Figure 2 on p. 379). Furthermore, Mimidipudi teaches that this signal transduction cascade interacts with the TrkA signaling pathways, and vice versa (see p. 375). There is no structural limitation on the transduction agent to be provided, or on the agents capable of interaction with the transduction agents. Furthermore, many of the members of the signal transduction pathway, when provided, would be expected to increase rather than decrease the activity of this pathway and the instant claims are all drawn to agents which inhibit the pathway. For example, providing sphingomyelinase would be expected to increase the production of ceramide (see Mamidpudi p. 380 second column), thus providing this transduction agent would result in augmentation, not inhibition of the signal transduction pathway. Because there are no structural limitations on the agents to be provided in claim 23, many of the agents in the pathway would be expected to be agonists and not inhibitors of the pathway, and the pathway itself is very complex, the skilled artisan would have to resort to an undue amount of experimentation in order to make and use commensurate in scope with the claims 23 and 30, for example.

Claim 25 is limited to certain interactions between specific components of the pathway, but like claim 23 does not provide any structural limitations. Similarly claim 26 does not provide any structural limitations. Even if the artisan identified agents capable of inhibiting one of the interactions in claims 25 or 26, there is no reason to believe that this agent would inhibit a p75 signal transduction pathway, which is recited in the parent claim (21). Many of the interactions recited in claims 25 and 26 appear in a plethora of pathways other than p75. For example, Rho and GDI are both involved in G-protein coupled receptor signal transduction pathways, but the

p75 pathway does not include a GPCR. Wettschureck (2002. J Mol Med 80:629-638) teaches that Rho is involved in many functions, including cellular adhesion and cytokinesis, is involved in many diverse diseases, and that the proteins which regulate Rho are found ubiquitously (see p. 631). Thus an agent which is capable of maintaining or enhancing an interaction between Rho and Rho GDI, or capable of inhibiting conversion of Rho GDP to Rho GTP, or capable of inhibiting interactions between Rho and Rho kinase, or capable of inhibiting an activity of Rho kinase, would not reasonably be expected to be an agent capable of inhibiting a p75 signal transduction pathway, as these molecules are involved in so many complex and diverse signal transduction pathways.

11. Claims 21 – 23 and 25 – 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to agents which are capable of inhibiting a p75 signal transduction pathway. Dependent claim 29 recites compositions comprising at least one of several agents, but many of these are referred to by function only and not by structure. The prior art teachings of Roux et al. (2002. Progress in Neurobiology 67:203-233) indicate that many different molecules, often with opposing functions, fall within the scope of these recitations (see for Example Figure 7 on p. 220). For example, TRAF6 and NADE both interact with p75, but the former leads to cell death while the latter leads to survival so it could not be the case that both of them inhibit the pathway. Thus recitations of the functions in claim 29, as well as similar recitations in claims 25 and 26, is not sufficient to provide description. Even a description of a function, namely that an agent interacts with certain molecules, does not describe to the artisan what the agent does. Interaction could include binding, promoting the activity (i.e. an agonist), or inhibiting the activity (i.e. an antagonist). Furthermore as Roux teaches the p75 pathway is complex and is involved in maintenance, survival, and death of neurons. So describing where an agent interacts is not sufficient to allow the artisan to conclude that applicant had in his possession the full genera as claimed.

Additionally the definition of instantly-elected Pep5 protein provided the paragraph bridging pp. 61 – 62 of the specification includes all variants and fragments of Pep5, provided that the fragments have biological activity. This is not a limiting definition of Pep5, as the terms

"variants" and "fragments" (defined on pp. 106 and 79, respectively) allow for unlimited substitutions and deletions, so long as a single amino acid remains from the original sequence. Furthermore the requirement that the variant or fragment retain biological activity is very broad as the definition provided on p. 61 - 62 is exemplary, not exclusive, and thus a Pep5 protein, as defined, could include any protein with at least one amino acid in common with SEQ ID NO:2 which is capable of producing antibodies, as this is a biological activity. Finally, this is not an explicit description of Pep5. While the specification discloses that SEQ ID NO:2 falls within the scope of the definition, the definition includes *any* peptide which binds to the intracellular domain to inhibit action of Rho by p75. The specification only provides evidence of possession of SEQ ID NO:2 and a variant thereof with a single residue added to the C-terminal end.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, there are not sufficient structure/function correlations presented in the specification to allow the skilled artisan to conclude that applicant possessed the invention as claimed. Claim 29, for example, includes molecules that can specifically interact with a Rho kinase or a Rho GDI, but there is not a requirement that any particular region of these molecules be bound, or what interactions are to occur. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genera of molecules, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v.*

Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Therefore the written description requirement has not been met.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 28 – 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 recites the limitation "wherein the nerve" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 29 is also deemed to be indefinite to the extent that it recites "a Pep5 polypeptide". The specification provides a definition for these polypeptides on p. 61 – 62. However a skilled artisan would not be able to determine what polypeptide sequences are Pep5 polypeptides, as the term is not defined in a limiting fashion. The definition is drawn to multiple different scopes and while it includes SEQ ID NO:2, it also includes any peptide which binds to the intracellular domain of p75 to inhibit activation of Rho by p75. This includes many molecules beyond the scope of SEQ ID NO:2 and minor substitutions to it; for example it also includes antibodies. Because the term is defined with differing scopes and there is not sufficient guidance as to what peptides are encompassed by the term, a skilled artisan would not be able to determine the metes and bounds of the claim.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 21 – 23 and 25 –29 are rejected under 35 U.S.C. 102(b) as being anticipated by Ilag (1999. Biochemical and Biophysical Research Communications 255:104-109).

Ilag et al. teach a protein sequence, which they call peptide 2, which is 100% identical to the protein applicant terms Pep5, i.e. SEQ ID NO:2 (see Ilag, p. 35106, first column). Ilag

teaches that this protein was identified in a phage display experiment where the intracellular domain of p75 was used as the bait (see p. 104). Ilag teaches that the method used identifies proteins which bind specifically with one another thus Ilag had identified Peptide 2 as a protein that binds specifically to the p75 intracellular domain. Ilag does not teach that the agent inhibits the signal transduction pathway, but this is an inherent property of the compound. Ilag also teaches the protein in LB medium, so it is in a composition. As this composition can be administered to neurons and specifically interacts with a transduction agent in the p75 pathway, the product anticipates claims 21 – 23 and 29.

As the remarks filed 25 July 2005 indicate that Pep5 polypeptides read on the functional limitations of claims 25 and 26, these claims stand rejected as well. The examiner acknowledges that Ilag is silent as to whether the protein composition has these properties but since a product and its properties are inseparable, and the prior art teaches the product, claims to inherent properties of the same product are also anticipated. As the composition was administered to E. coli, it is suitable for both in vivo and in vitro administration, and thus meets the limitations of claim 27. Claim 28 stands rejected because it does not limit claim 21 and the prior art product meets the limitations of claim 21.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 21 – 23 and 25 – 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ilag, Schwarze (1999. Science 285:1569 – 1572), Voet (Biochemistry, Second Edition,

1995. pp. 58 – 59), and Bertin (U.S. Patent Application Publication 2002/0061833, published 23 May 2002, filed 26 December 2000).

The reasons why Ilag meets the limitations of claims 21 – 23 and 25 – 29 are discussed in the rejection under 102(b) above and will not be reiterated herein. Ilag teaches that their protein binds to the death domain of the p75 receptor (see paragraph spanning pp. 106 – 108). Ilag does not teach the Peptide 2 (which applicant calls Pep5) bound to a PTD domain.

Schwarze teaches fusing proteins to the PTD domain of TAT for intracellular delivery of protein. Schwarze teaches that the method is effective for proteins of a wide range of sizes and does not depend on the structure or function of the protein that is being bound to PTD. It would have been obvious to one of ordinary skill in the art to bind the protein from Ilag to the PTD domain, as taught by Schwarze, with a reasonable expectation of success. The motivation to do so would be to aid in crossing the cell membrane thereby inhibiting cell death, as Bertin teaches that proteins which bind to the intracellular domain of p75 inhibit cell death (see p. 8 paragraph 0092 and p. 9 paragraph 0112). Ilag teaches that the protein binds to the death domain of p75, which is part of the intracellular region of this protein, and Schwarze teaches that proteins greater than 600 daltons do not enter cells. Voet provides the weight of all twenty amino acids that are used in proteins and provides evidence that the Peptide 2 protein from Ilag is too large to enter the cell. Thus the artisan would be motivated to modify the Peptide 2 protein to allow it to bind to the death domain, thereby inhibiting cell death.

Conclusion

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
October 6, 2005

SHARON TURNER, PH.D.
PRIMARY EXAMINER
10-11-05